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Grau de Química

Treball Final de Grau

Ruthenium complexes with phosphines containing the 1-pyrenyl substituent.

Complexos de ruteni amb fosfines que contenen el grup 1-pirenil.

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A falta de argón, bueno es nitrógeno.

Andrés Herran

Als meus pares i a la Laura per estar incondicionalment al meu costat.

M'agradaria agrair al Dr. Guillermo Muller tots els seus consells i que sempre tingués una mà per ajudar-me, al Albert Gallen pels moments dins i fora del laboratori fent-me tota aquesta etapa més fàcil. A tota la gent del departament per acollir-me tan bé i calmar-me en els moments de drama, gràcies per ser tan bons amb mi.

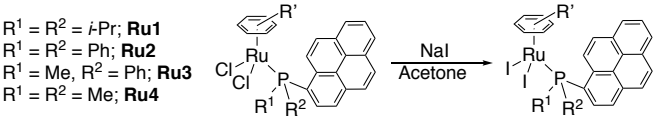
I finalment però no per això menys important al Dr. Arnald Grabulosa, per tots els moments compartits, riures i friquismes, però sobretot per la seva infinita paciència i pels seus consells pipàrrics que m'han fet tenir una estada molt especial.

REPORT

CONTENTS

1. SUMMARY

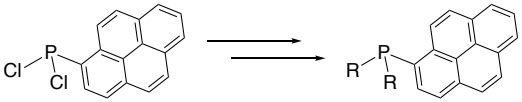
The synthesis of eight Ru complexes with the general formula **[RuI$_2$(η^6-arene)(PPyrR$_2$)]** (Pyr = 1-pyrenyl; arene = methyl benzoate or *p*-cymene), is described. These species were obtained from the parent dichlorocomplexes by treatment with an excess of sodium iodide in refluxing technical acetone for a period between 4 h and 11 days depending on the complex.



Ru1-Ru4 stands for *p*-cymene complexes while **Ru1'-Ru4'** are methyl benzoate complexes.

Their structures were confirmed by IR, multinuclear NMR (^{31}P, ^{1}H, ^{13}C), MS, EA and in three cases by single crystal X-ray diffraction. The antitumoral activity of these iodinated ruthenium complexes was studied against several cell lines and the results are promising compared to the chlorocomplexes.

The synthesis of five new (1-pyrenyl)phosphines is also described. These ligands were designed taking into account the relation between the antitumoral activity and the bulkiness of the phosphines in dichlorocomplexes. The ligands have been obtained from the known dichlorophosphine **L0**.



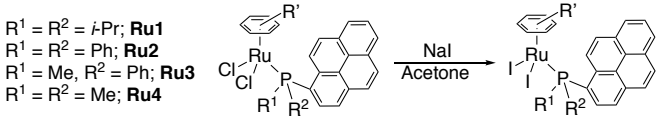
L0 **L4-L8**

These phosphines were prepared adapting literature methods and have been characterised by the usual techniques.

Keywords: Ruthenium complexes, pyrenyl phosphines, iodinated complexes, antitumoral metallodrugs, organometallics, bioorganometallic chemistry.

2. RESUM

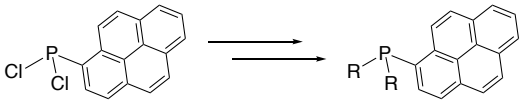
En aquest projecte es descriu la síntesi de vuit complexos de ruteni amb fórmula general **[RuI$_2$(η^6-arè)(PPyrR$_2$)]** (Pyr = 1-pirenil; arè = benzoat de metil o *p*-cimè). Aquests compostos es van obtenir a partir dels diclorocomplexos per tractament amb un excés de iodur de sodi en acetona a reflux durant un període entre 4 h i 11 dies depenent del complex.



Ru1-Ru4 són els complexos amb *p*-cimè mentre **Ru1'-Ru4'** els de benzoat de metil.

Les estructures dels complexos s'han pogut confirmar mitjançant IR, RMN multinuclear (^{31}P, ^{1}H, ^{13}C), MS, EA i per difracció de raig X de monocristall per tres dels compostos. L'activitat antitumoral d'aquests complexos iodats s'ha estudiat en diferents línies cel·lulars i és prometedora comparat amb els complexos clorats.

També es descriu la síntesi de cinc noves (1-pirenil)fosfines, les quals es van dissenyar per la relació estructura-activitat que presentaven els lligands en els complexos clorats anàlegs. Tots ells es van obtenir a partir del precursor diclorofosfina ja conegut **L0**.



L0 **L4-L8**

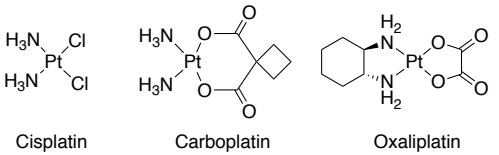
La preparació d'aquestes fosfines es va dur a terme adaptant altres síntesis ja conegudes en la bibliografia. Aquests lligands es van caracteritzar per les tècniques habituals.

Paraules clau: Complexos de ruteni, pirenilfosfines, complexos iodats, metal·lofàrmacs antitumorals, compostos organometàl·lics, química bioorganometàl·lica.

3. INTRODUCTION

In developed countries cancer is the second cause of death only after cardiovascular diseases whereas it is the third cause in developing ones. What is even worse is that the number of cancer deaths is continuously increasing. For that reason, many chemotherapeutic drugs have been synthetised to improve the survival rate. Some of these drugs are based on organic scaffolds but another important group are metallodrugs based on transition metals.[1]

In 1965 Rosenberg[2] discovered that cisplatin had inhibited cell division in bacteria. Soon after it was found that this compound also presented a potent antitumoral effect and in 1978 it was approved as a chemotherapeutic drug against testicular and ovarian cancers. Nowadays platinum complexes are widely considered an achievement in the field of cancer treatment by chemotherapy and are still one of the most used type of metallodrugs (Scheme 1).

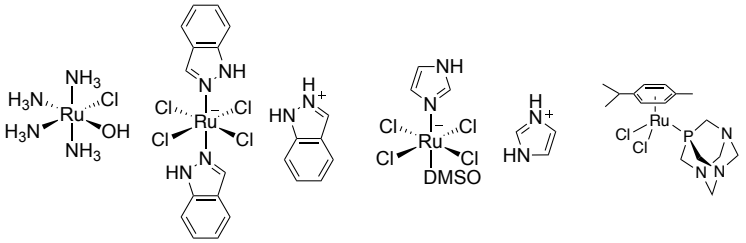


Scheme 1. The most used chemotherapeutic platinum drugs.

Despite the success of cisplatin and derivatives, these compounds present severe side-effects (nephrotoxicity, neurotoxicity and ototoxicity…) and frequently tumoral cells develop resistance. In order to improve the antitumoral activity and reduce the side-effects, many other coordination compounds have been tested.

Among the variety of metals that have been explored, it was found the exchange reaction in ruthenium complexes (specially aquation, which is very important for cytoxicity) are similar than the platinum ones and for that reason ruthenium-based systems have been studied in depth.[3] Additionally these compounds have shown other promising features, such as reduced toxicity and increased selectivity towards cancer cells than platinum. These advantages are believed to be due to the similarity between ruthenium and iron. In addition ruthenium metallodrugs present antimetastatic properties.

Some of the most important ruthenium compounds developed to date are shown in Scheme 2.

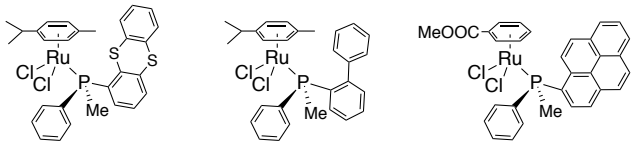


Scheme 2. Publication date of the most studied ruthenium chemotherapeutic drugs.

The two lead ruthenium complexes are NAMI-A and KP1019, which are about to become marketable drugs due to their high selectivity against tumors. Regardless their differences, both are Ru(III) compounds that are believed to become active by reduction to Ru(II) species in the reducing tumoral medium.

For that reason Ru(II) compounds stabilised by a η^6-coordinated arene ligand were directly used.[1b,3b,3c,4] The most important, which present clinical studies, are the RAPTA family.[5] These neutral type of complexes are saturated (18 e^-) with an octahedral geometry, which present a ligand disposition and are typically known as 'piano-stool'. This name stems from the arene being the seat and the two chlorides and the phosphine the legs of the stool.

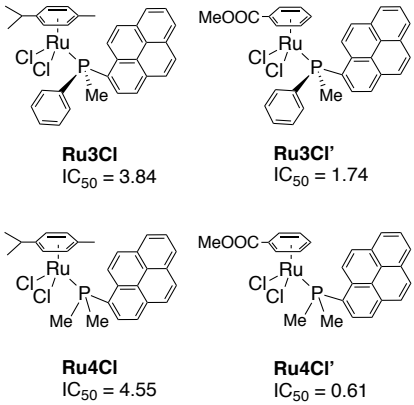
The Homogeneous Catalysis group at the University of Barcelona developed a large number of complexes with general formula **$[RuCl_2(\eta^6\text{-arene})(PR_3)]$** with PR_3 being a *P*-stereogenic phosphine and have been used in asymmetric reduction of ketones.[6] Given the similarity of these complexes with the RAPTA family, many of them were tested as antitumoral agents in collaboration with the Bioinorganic Chemistry group.[6b] It was found that the complexes with phosphines containing the aromatic polycyclic substituent 1-pyrenyl present the highest activity (Scheme 3).[7]



RuA IC_{50} = 16.28 **RuB** IC_{50} = 10.33 **Ru3Cl'** IC_{50} = 1.74

Scheme 3. IC50 values (μM) against SW620 (human colon carcinoma) cell line.

For that reason a second generation of achiral 1-pyrenylphosphines was prepared and coordinated to the ruthenium precursors. After the antitumoral activity studies, structure-activity relationships were discovered. Regarding the phosphine, the more hindered produce the lowest activity while the *p*-cymene compounds are less active than the methyl benzoate analogues as is shown by the selected examples in the Scheme 4.



Ru3Cl IC_{50} = 3.84 **Ru3Cl'** IC_{50} = 1.74

Ru4Cl IC_{50} = 4.55 **Ru4Cl'** IC_{50} = 0.61

Scheme 4. IC_{50} values of Ru complexes against the SW620 (human colon carcinoma) cell line.

Therefore the most active complex was found to be **Ru4Cl'** bearing the less hindered dimethylphosphine and methyl benzoate. As it can be seen this precursor presents very promising cytotoxicity in the low μM range.

From the literature it was found that in some cases changing chloride by iodide in ruthenium complexes produce more cytotoxic systems.[8] Therefore it seemed logical to prepare a third generation of complexes with the general formula **[RuI$_2$(η^6-arene)(PPyrR$_2$)]** and test their antitumoral effect.

This Final Project describes the work carried out on these new ruthenium compounds for use in biological studies, and the design of new unhindered 1-pyrenylphosphine ligands.

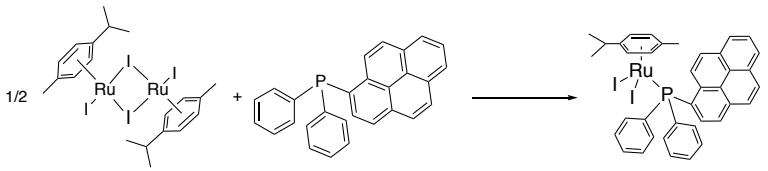
4. OBJECTIVES

- Synthesis and characterization of **[RuI$_2$(η^6-arene)(PPyrR$_2$)]**, where arene is methyl benzoate or *p*-cymene and R is methyl, isopropyl or phenyl.
- Synthesis and characterization of new 1-pyrenylphosphines (**L4** – **L8**) from the already known dichloro(1-pyrenyl)phosphine (**L0**).

5. RESULTS AND DISCUSSION

5.1. SYNTHESIS OF [$RuI_2(\eta^6$-ARENE)(PPYRR_2)]

The first experiment was started by mixing **L2** and **D1** in dichloromethane following the typical procedure to prepare this kind of complexes (Scheme 5).[6e]



D1 **L2** **Ru2I**

Scheme 5. Preparation of **Ru2I** by splitting of **D1**.

After the work-up the crude was analysed by $^{31}P\{H\}$, which showed a major peak at 23.4 ppm accompanied by another resonance at 18.1 ppm and many other small peaks due to the oxidation and hydrolysis of the phosphine. The recrystallisation of the crude gave a solid whose $^{31}P\{^1H\}$ NMR showed the two peaks in a 1:0.7 ratio. As it will be shown below, the peak at lower field corresponds to **Ru2I**, while the identity of the other compound remains a mystery. Since the desired product could not be obtained pure by this method an alternative one was envisaged.

The second strategy was to exchange the Cl ligands of **Ru1Cl'** by I. To this end, this complex was dissolved in dichloromethane and vigorously stirred with concentrated aqueous KI, forming a biphasic system.[9] The reaction was successful and after 72 h the pure desired product **Ru1I'** was isolated in 49% yield. Unfortunately, when the same conditions were applied to **Ru2Cl'** a 1:2 ratio between **Ru2Cl'** and **Ru2I'** respectively was observed after a week. As the last attempt, the reaction mixture was heated for 16 h at 45 ºC, but the product ratio remained unchanged.

Finally, the exchange reaction was performed in acetone at reflux, following the method of Hudson and Simpson.[10] The first complex attempted was **Ru1Cl'**, hence the complex and a large excess of NaI were dissolved in technical grade (not dry) acetone and lead to reflux for

several hours. Interestingly if extra pure acetone was used, the reaction was slower, therefore the presence of water probably speeds up the reaction.

The reaction time needed to reach full conversion depended strongly on the complex (Table 1).

Complexes	t (h)
Ru1	4
Ru1'	16
Ru2	4
Ru2'	16
Ru3	4
Ru3'	72
Ru4	24
Ru4'	264 (11 days)

Table 1. Reaction times required to reach full conversion.

From the table it can be concluded the bulkiness of the phosphine and the electronic nature of the η^6 coordinated arene ring affects the exchange rate.

Fortunately the reactions could be easily monitored by ^{31}P NMR spectroscopy, for example Figure 1 shows the evolution of the exchange reaction for **Ru4Cl'**.

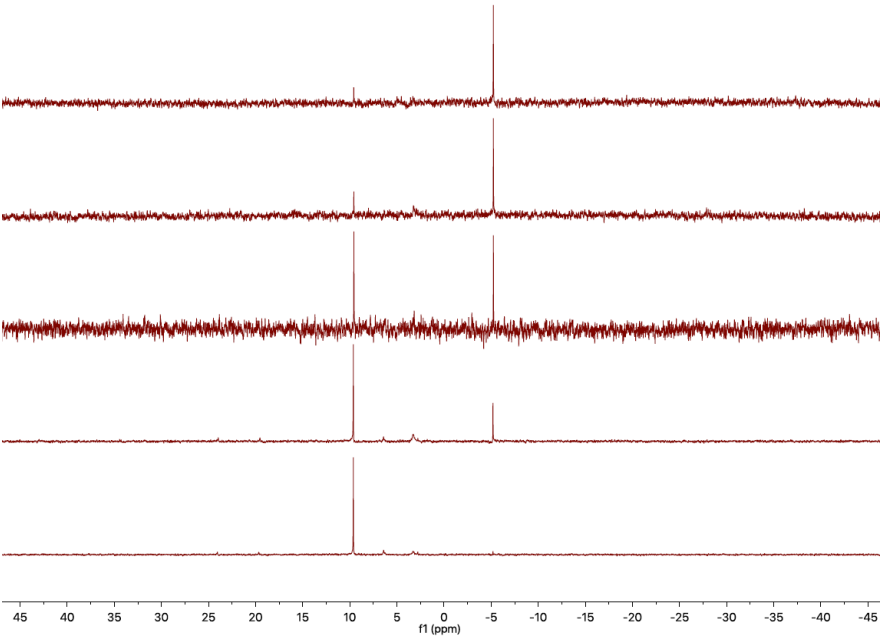


Figure 1. ^{31}P NMR monitoring of the exchange reaction from **Ru4Cl'** (+9.6 ppm) to **Ru4I'** (–5.2 ppm). Bottom to top: 1, 2, 3, 7 and 11 days.

For an 18-electron octahedral complex a dissociative mechanism for ligand exchange reactions can be envisaged. In this kind of mechanisms the rate-limiting step is the departure of a ligand, consequently, the bulkier the ancillary ligand, the faster the exchange. This fits with the fact that the exchange in complexes **Ru4** and **Ru4'**, bearing dimethyl phosphine (the less hindered ligand) needs a longer reaction time. The crowding, however, is not the only important factor, the electronic nature of the arene also affects the rate. It can be expected that electron-richer arenes should make the Ru-arene bond stronger which, in turn, should make the Ru-Cl bond weaker, increasing the reaction rate. This is in accordance with the observation that the *p*-cymene complexes react faster.

The complexes were obtained after an extractive work-up and recrystallisation as brown dusty solids in yields between 37 and 75 %. Those complexes requiring longer reaction time had the lowest yields.

This type of complexes have been fully characterised by the usual techniques. Mass Spectrometry (MS) displayed the same characteristic m/z peak corresponding to $[M - I]^+$ analogously to the chlorocomplexes described in the literature.[6e] As expected the IR of **Ru1I'**-**Ru4I'** showed a strong band around 1730 cm^{-1} due to C=O stretching of the carboxylate.

^{31}P NMR spectroscopy showed a single resonance for all complexes shifted to higher fields from the parent chlorocomplexes (Table 2).

Complexes	Cl_2	I_2	$\Delta\delta$
Ru1	+36.3	+31.3	-5
Ru1'	+38.9	+34.5	-4.4
Ru2	+32.1	+23.4	-8.7
Ru2'	+32.1	+22.4	-9.7
Ru3	+17.2	+10.3	-6.9
Ru3'	+16.7	+9.7	-7.0
Ru4	+7.7	-5.8	-13.5
Ru4'	+9.6	-5.2	-14.8

Table 2. ^{31}P chemical shifts of ruthenium complexes.

Owing to the lower electronegativity of iodine compared to chlorine, the P atoms in iodocomplexes appear more shielded.

In ^1H NMR spectra there are 3 regions of chemical shifts: the highest shift which is part of aromatic zone (9.5 – 7.5 ppm), followed by the coordinated arene (5.5 – 4.0 ppm) and finally there is the aliphatic region (4.0 – 0.5 ppm). As an example, Figure 2 shows the ^1H NMR spectrum of complex **Ru4I**.

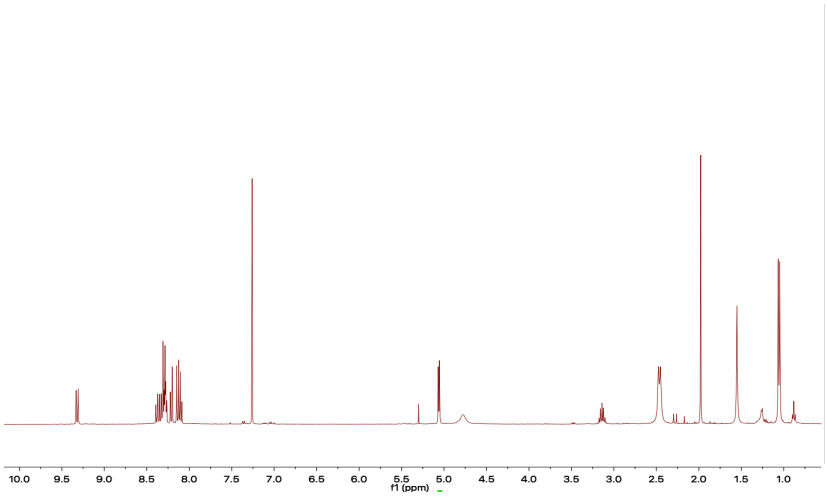


Figure 2. ^{1}H NMR spectrum of complex **Ru4l**.

Only one of the phosphines (**L3**) is chiral, so it is expected for **Ru3l** and **Ru3l'** to have all the protons non-equivalent. The reason is that these complexes do not have any symmetry element.

This is indeed the case and hence four and five resonances can be observed in the arene coordinated region for **Ru3l** and **Ru3l'** respectively.

On the other hand, the phosphines of the rest complexes are achiral, so the ^{1}H NMR spectra some of the protons should be equivalent. This supposition is correct except interestingly in the case of complexes **Ru1**, in which all the protons are non-equivalent, like **Ru3**. This may be due to the bulkiness of **L1**, which could slow down the rotation of the arene.

Similar trends could be observed in ^{13}C NMR spectra, which could be assigned thanks to bidimentional ^{1}H – ^{13}C HSQC experiments.

Single crystals, suitable for X-ray crystallography, could be obtained for complexes **Ru2l'**, **Ru3l** and **Ru4l** by diffusion of hexane into dichloromethane solutions of the complexes. The diffraction experiments were performed in the Advanced Light Source synchrotron facility of the Berkeley University. The representation of their molecular structures is given in Figure 3 and selected metric parametres in Table 3.

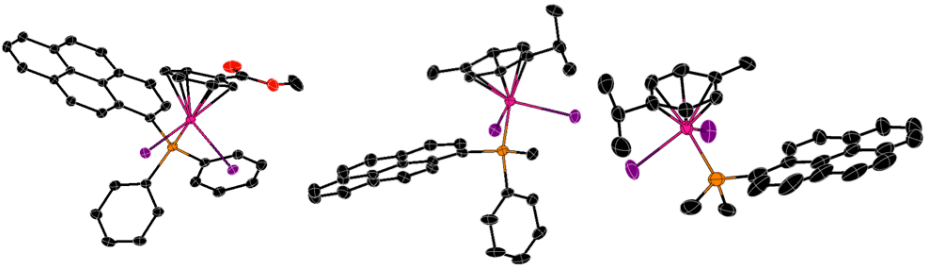


Figure 3. From left to right: ORTEP representations of **Ru2I'**, **Ru3I** and **Ru4I** with the thermal ellipsoids drawn at the 50% probability level and H atoms omitted for clarity.

As expected the complexes adopt the typical three-legged piano stool geometry. The 1-pyrenyl group of the phosphine point outwards the ruthenium center, probably due to steric reasons. In complex **Ru3I** the phosphine would have *S* absolute configuration as a free ligand, as expected.[11]

Parameter	Ru2I'	Ru3I	Ru4I
Ru–I	2.7127(3) 2.7128(3)	2.7145(5) 2.7189(6)	2.7153(8) 2.7364(7)
Ru–P	2.3814(7)	2.3470(14)	2.346(2)
P–C_{Pyr}	1.836(3)	1.839(6)	1.837(12)
P–C_{Ph}	1.837(3) 1.830(3)	1.842(6)	–
P–C_{Me}	–	1.831(6)	1.813(10) 1.835(10)
P–Ru–I	91.19(2) 91.87(2)	90.85(4) 93.21(4)	91.72(6) 86.91(7)
I–Ru–I	86.482(10)	88.063(16)	86.44(3)

Table 3. Selected distances (Å) and angles (º) for complexes **Ru2I'**, **Ru3I** and **Ru4I**.

Distances and angles are in the normal range for this type of complexes. It is observed that the bulkier the phosphine, the longer the Ru–P distance. Interestingly the Ru–I distances are considerably larger than Ru–Cl of related complexes.[6a,6c,6e]

Preliminary studies were carried out on the cytotoxicity of iodinated ruthenium compounds to compare with the parent chlorocomplexes. Table 4 gives the IC_{50} values of **Ru1I** and **Ru1Cl** against SW620 (human colon carcinoma), A375 (human melanoma) and MCF7 (breast carcinoma).

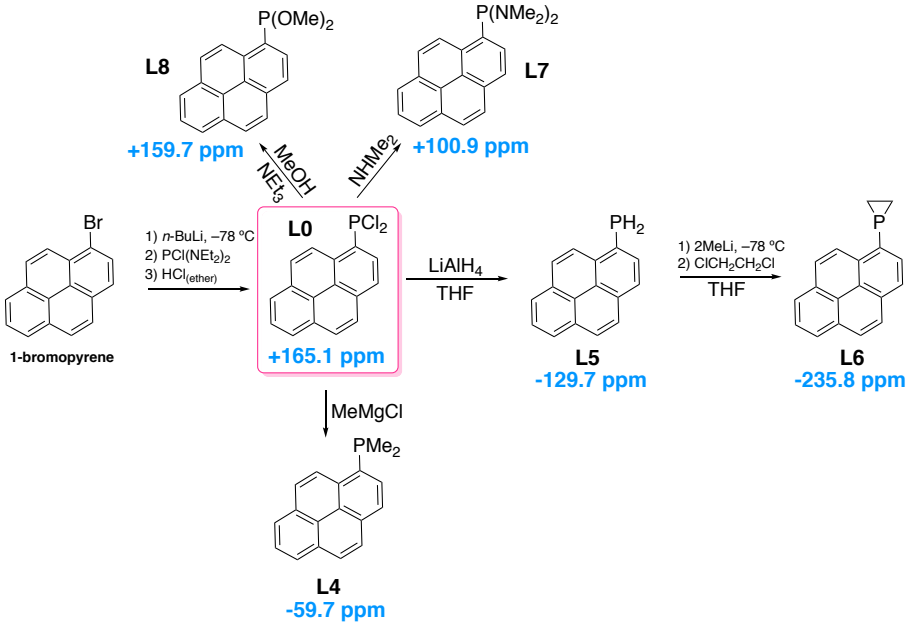
Complexes	SW620	A375	MCF7
Ru1Cl	13.41	16.58	22.96
Ru1I	6.44	9.18	10.56

Table 4. IC_{50} values of **Ru1I** and **Ru1Cl**.

Encouragingly, the table shows that **Ru1I** is approximately twice as active compare to **Ru1Cl**. Taking into account that **Ru1** is the less active, much better results can be expected for the rest of the iodocomplexes. These studies are currently underway.

5.2. SYNTHESIS OF NEW 1-PYRENYLPHOSPHINES

After the successful synthesis of the ruthenium compounds, the synthesis of new phosphines was undertaken following literature methods for similar ligands. The 1-pyrenylphosphines prepared are shown in Scheme 6.



Scheme 6. Preparation of 1-pyrenylphosphines with their chemical shift.

The synthesis of **L0** was adapted from the method described by Baumgartner and coworkers.[12] **L0** is a versatile synthon owing to the reactivity of the P-Cl bond with nucleophilic species. Our aim, as discussed in the Introduction, was to obtain new $PPyrR_2$ where R is an unhindered group.

To obtain **L0**, 1-bromopyrene was lithiated at low temperature and the formed 1-pyrenyllithium was reacted with bis(diethylamino)chlorophosphine, producing bis(diethylamino)(1-pyrenyl)phosphine, which was detected as a singlet at +100 ppm in ^{31}P NMR. This compound was hydrolysed with dry hydrogen chloride in diethyl ether, which yielded the desired product as a yellow solid.[12]

Reacting **L0** with dimethylamine or methanol in the presence of NEt_3, **L7** and **L8** were obtained respectively, after the filtration of the ammonium salts.[13] These products were isolated and characterised and their ^{31}P chemical shifts were in the similar range of other related compounds[13]. In ^{1}H NMR is observed that the methyl groups are equivalent and appear as doublets due to the coupling with the phosphorus.

The reaction of **L0** with MeMgCl cleanly afforded the known ligand **L4**,[7] which was detected as a singlet at –60 ppm in ^{31}P NMR and was directly used for the synthesis of **Ru4**. Interestingly, using MeMgCl instead of the pyrophoric chlorodimethylphosphine makes easier the synthesis of these complexes.

If **L0** is reacted with lithium aluminium hydride, the primary phosphine (**L5**) is obtained and appears at –129.7 ppm in ^{31}P NMR spectrum (Figure 4).[14]

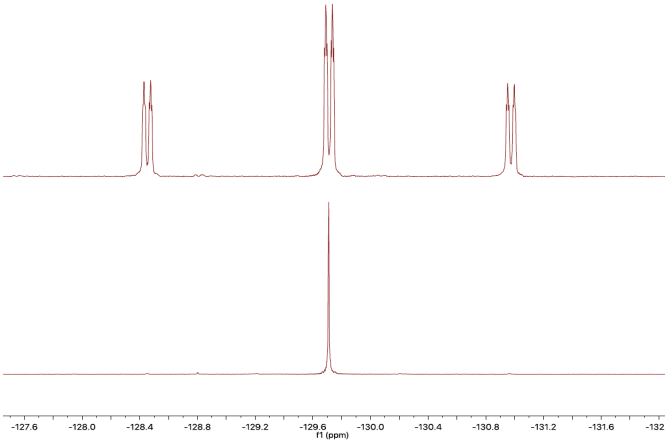


Figure 4. Comparison of ^{31}P (top) and $^{31}P\{^{1}H\}$ (bottom) of **L5**.

In this case the ^{1}H-coupled ^{31}P NMR was also recorded. As expected a triplet with a $^{1}J_{PH}$ of 204 Hz was found, but it had a fine structure of doublet of triplets, due to the coupling with the pyrenyl protons.

To obtain the phosphirane (**L6**), **L5** was deprotonated with methyllithium and the dianion was treated with 1,2-dichloroethane.[13,14c] The compound **L6** was isolated and characterised and in the ^{31}P NMR appears as a singlet at –236 ppm, a chemical shift typical for this kind of phosphines.[13,14c] Two multiplets of two protons are observed in ^{1}H NMR.

6. EXPERIMENTAL SECTION

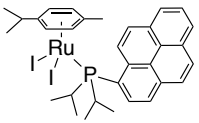
6.1. MATERIALS AND METHODS

All compounds were prepared under a purified nitrogen atmosphere by standard Schlenk and vacuum-line techniques. The solvents were obtained from solvent-purification system or purified by standard procedures and kept under nitrogen. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and HSQC ^{1}H-^{13}C NMR spectra were recorded with 400 MHz spectrometers with $CDCl_3$ as solvent unless otherwise specified. The IR spectra were recorded in KBr, and the main absorption bands are expressed in cm^{-1}. High-resolution mass spectrometry analyses were performed with electrospray ionisation. Elemental C, H analyses were performed at the Centres Científics i Tecnològics (CCiT) of the Universitat de Barcelona.

6.2. PREPARATION OF RUTHENIUM COMPLEXES

6.2.1. Ru1I

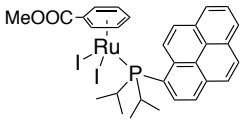
A suspension of **Ru1Cl** (423 mg, 0.68 mmol) and NaI (1.5 g, 10 mmol) in technical grade acetone (40 mL) was heated under reflux for 4 h protected from light. The solvent was removed under reduced pressure and the crude was extracted with dichloromethane/water. The combined organic phase was dried with anhydrous Na_2SO_4 and filtered. After elimination of the solvent, the crude was crystallised from dichloromethane and hexane and finally washed with pentane. Yield 410 mg (75%).



Brown solid. **IR**: 2952, 2926, 2870, 1448, 1200, 1026, 848, 609, 509. **$^{31}P\{^{1}H\}$ NMR**: δ +31.3 (s). **^{1}H NMR**: δ 8.96 (d, *J* = 9.6, 1H), 8.51 (t, *J* = 8.4, 1H), 8.32-8.23 (m, 4H), 8.20 (d, *J* = 8.8, 1H), 8.13 (d, *J* = 10.0, 1H), 8.09 (d, *J* = 7.6, 1H), 5.50 (s, br, 1H), 4.86 (s, br, 1H), 4.70 (s, br, 1H), 4.40 (s, br, 1H), 4.27 (s, br, 1H), 3.54 (s, br, 1H), 3.34 (sept, *J* = 6.8, 1H), 1.85 (s, br, 3H), 1.69 (s, 3H), 1.67 (s, br, 3H), 1.43 (s, br, 3H), 1.26 (s, br, 3H), 0.96 (s, br, 3H), 0.63 (s, br, 3H). **$^{13}C\{^{1}H\}$ NMR**: δ 133.2-123.1 (C, CH, Ar), 87.8-86.5 (4CH), 31.2 (CH), 23.7 (br, $2CH_3$), 21.8 (br, CH_3), 20.2 (br, CH_3), 19.6 (br, CH_3), 18.9 (CH_3), 18.7 (br, CH_3), **HRMS** (ESI): *m/z* calc. for $C_{32}H_{37}IPRu$ $[M - I]^+$ 681.0715; found 681.0720. **EA**: calc. for $C_{32}H_{37}I_2PRu$ C (47.60%), H (4.62%); found C (45.71%), H (4.74%).

6.2.2 Ru1I'

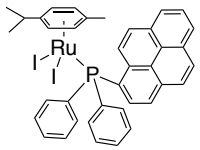
The procedure was the same used to obtain **Ru1I** but starting from **Ru1Cl'** (470 mg, 0.75 mmol) and keeping the reaction 16 h at reflux. Yield: 435 mg (72%).



Brown solid. **IR**: 3052, 2961, 2926, 2865, 1735, 1430, 1296, 1265, 1104, 848, 761, 604. **^{31}P{^{1}H} NMR**: δ +34.5 (s). **^{1}H NMR**: δ 9.03 (d, *J* = 9.2, 1H), 8.52 (t, *J* = 8.4, 1H), 8.34-8.20 (m, 5H), 8.15-8.10 (m, 2H), 6.49 (t, *J* = 5.6, 1H), 6.37 (d, *J* = 5.6, 1H), 5.24 (t, *J* = 5.6, 1H), 4.55 (dd, *J* = 9.6, *J* = 5.2, 1H), 4.39 (t, *J* = 5.2, 1H), 4.26 (dd, *J* = 14.0, *J* = 6.8, 1H), 3.98 (s, 3H) , 3.57 (dd, *J* = 14.8, *J* = 7.6, 1H), 1.85 (dd, *J* = 16.4, *J* = 7.6, 3H), 1.71 (dd, *J* = 11.2, *J* = 7.2, 3H), 1.46 (dd, *J* = 16.0, *J* = 7.2, 3H), 0.66 (dd, *J* = 13.2, *J* = 7.2, 3H). **^{13}C{^{1}H} NMR**: δ 164.4 (CO), 133.4-123.7 (C, CH, Ar), 93.6 (CH), 93.2 (CH), 90.3 (CH), 89.0 (d, *J* = 9.4, C), 86.9 (CH), 83.6 (CH), 53.7 (CH_3), 30.3 (d, *J* = 25.7, CH), 29.4 (d, *J* = 25.3, CH), 23.2 (CH_3), 20.1 (d, *J* = 7.0, CH_3), 19.8 (d, *J* = 7.2, CH_3), 18.3 (CH_3). **HRMS** (ESI): *m/z* calc. for $C_{30}H_{31}O_2IPRu$ $[M - I]^+$ 683.0144; found 683.0142.

6.2.3 Ru2I

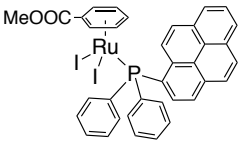
The procedure was the same used to obtain **Ru1I** but starting from **Ru2Cl** (450 mg, 0.68 mmol) and keeping the reaction 4 h at reflux. Yield: 369 mg (62%).



Brown solid. **IR**: 3048, 2957, 2917, 2861, 1470, 1430, 1374, 1087, 852, 687, 635, 539, 513, 461. **^{31}P{^{1}H} NMR**: δ +23.4 (s). **^{1}H NMR**: δ 8.62 (d, br 1H), 8.28 (d, *J* = 7.2, 1H), 8.23-8.05 (m, 6H), 7.96 (d, *J* = 9.2, 1H), 7.73 (s, br, 4H), 7.35 (s, br, 6H), 5.43 (s, br, 2H), 4.67 (s, br, 2H), 3.53 (sept, *J* = 6.8, 1H),1.79 (s, 3H), 1.23 (s, br, 6H). **^{13}C{^{1}H} NMR**: δ 135.2-123.5 (C, CH, Ar), 112,6 (d, *J* = 5.9, C), 100.7 (C), 88.5 (d, *J* = 3.8, 2CH), 88.0 (2CH), 31.9 (CH), 22.7 (br, $2CH_3$), 19.0 (CH_3). **HRMS** (ESI): *m/z* calc. for $C_{38}H_{33}IPRu$ $[M - I]^+$ 749.0402; found 749.0413. **EA**: calc. for $C_{38}H_{33}I_2PRu$ C (52.13%), H (3.80%); found C (51.80%), H (3.92%).

6.2.4 Ru2I'

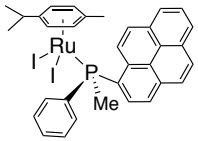
The procedure was the same used to obtain **Ru1I** but starting from **Ru2Cl'** (493 mg, 0.71 mmol) and keeping the reaction 16 h at reflux. Yield: 373 mg (60%).



Brown solid. **IR**: 3065, 2917, 1726, 1435, 1287, 1109, 857, 709, 517. **^{31}P{^{1}H} NMR**: δ +22.4 (s). **^{1}H NMR**: δ 8.74 (d, *J* = 9.2, 1H), 8.31-8.03 (m, 7H), 7.81-7.10 (m, 11H), 6.50 (s, br, 2H), 5.04 (s, br, 2H), 4.94 (m, 1H), 3.99 (s, 3H). **^{13}C{^{1}H} NMR**: δ 164.2 (CO), 135.5-123.9 (C, CH, Ar), 90.9 (3CH), 88.3 (2CH), 53.3 (CH_3). **HRMS** (ESI): *m/z* calc. for $C_{36}H_{27}IO_2PRu$ $[M - I]^+$ 750.9831; found 750.9862. **EA**: calc. for $C_{36}H_{27}I_2O_2PRu$ C (49.28%), H (3.10%); found C (48.98%), H (3.31%).

6.2.5 Ru3I

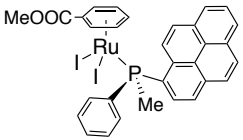
The procedure was the same used to obtain **Ru1I** but starting from **Ru3Cl** (150 mg, 0.24 mmol) and keeping the reaction 8 h at reflux. Yield: 93 mg (48%).



Brown solid. **IR**: 2952, 2917, 1638, 1618, 1439, 1384, 1026, 895, 849, 718, 629. **^{31}P{^{1}H} NMR**: δ +10.3 (s). **^{1}H NMR**: δ 8.80 (d, *J* = 12.8, *J* = 8.0, 1H), 8.30-7.75 (m, 10H), 7.43-7.33 (m, 3H), 5.50 (d, *J* = 6.0, 1H), 5.35 (d, *J* = 4.4, 1H), 5.17 (d, *J* = 6.8, 1H), 5.12 (d, *J* = 6.0, 1H), 3.04 (m, 1H), 2.81 (d, *J* = 9.6, 3H), 2.32 (s, 3H), 0.74 (d, *J* = 7.2, 3H), 0.42 (d, *J* = 6.8, 3H). **^{13}C{^{1}H} NMR**: δ 133.4-123.8 (C, CH, Ar), 110,6 (C), 96.8 (C), 91.4 (CH), 89.2 (CH), 88.4 (CH), 83.9 (CH), 31.6 (CH), 23.22 (d, *J* = 38.9, CH_3), 22.7 (CH_3), 20.4 (CH_3), 19.4 (CH_3). **HRMS** (ESI): *m/z* calc. for $C_{33}H_{31}I_2PRu$ $[M - I]^+$ 687.0246; found 687.0248. **EA**: calc. for $C_{33}H_{31}I_2PRu$ C (48.73%), H (3.84%); found C (50.11%), H (4.16%).

6.2.6 Ru3I'

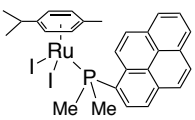
The procedure was the same used to obtain **Ru1I** but starting from **Ru3Cl'** (301 mg, 0.48 mmol) and keeping the reaction 4 h at reflux. Yield: 210 mg (54%).



Brown solid. **IR**: 2904, 2848, 1731, 1638, 1618, 1434, 1384, 1275, 1114, 616. **^{31}P{^{1}H} NMR**: δ +9.7 (s, br). **^{1}H NMR**: δ 8.74 (dd, *J* = 12.8, *J* = 8.0 1H), 8.34-7.95 (m, 8H), 7.79-7.74 (m, 2H), 7.41-7.31 (m, 3H), 6.51 (d, *J* = 6.4, 1H), 6.30 (s, br, 1H), 5.60 (t, *J* = 4.0, 1H), 5.33 (t, *J* = 6.0, 1H),), 5.06 (s, br, 1H), 3.85 (s, 3H), 2.90 (d, *J* = 10.4, 3H. **^{13}C{^{1}H} NMR**: δ 164.5 (CO), 133.6-124.0 (C, CH, Ar), 93.1 (CH), 93.1 (CH), 90.2 (CH), 87.4 (CH), 87.2 (CH) 86.3 (CH), 53.1 (CH_3), 23.7 (d, *J* =35.2, CH_3). **HRMS** (ESI): *m/z* calc. for $C_{31}H_{25}O_2IPRu$ $[M - I]^+$ 688.9674; found 688.9682.

6.2.7 Ru4I

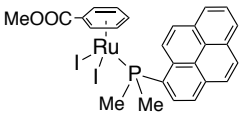
The procedure was the same used to obtain **Ru1I** but starting from **Ru5Cl** (230 mg, 0.40 mmol) and keeping the reaction 24 h at reflux. Yield: 206 mg (68%).



Brown solid. **IR**: 2957, 2917, 1624, 1430, 1383, 913, 845, 719, 698, 600, 532. **^{31}P{^{1}H} NMR**: δ –5.8 (s). **^{1}H NMR**: δ 9.32 (d, *J* = 9.6, 1H), 8.40-8.09 (m, 8H), 5.06 (d, *J* = 6.0, 2H), 4.78 (s, br, 2H), 3.14 (sept, *J* = 6.8, 1H), 2.46 (d, *J* = 9.2, 6H), 1.98 (s, 3H), 1.06 (d, *J* = 7.2, 6H). **^{13}C{^{1}H} NMR**: δ 133.2-123.8 (C, CH, Ar), 110,6 (C) 97.3 (C), 90.1 (d, *J* = 15.6, 2CH), 85.2 (br, 2CH), 31.7 (CH), 22.4 (br, $4CH_3$), 19.9 (CH_3). **HRMS** (ESI): *m/z* calc. for $C_{28}H_{29}IPRu$ $[M - I]^+$ 625.0089; found 625.0090. **EA**: calc. for $C_{28}H_{29}I_2PRu$ C (44.76%), H (3.89%); found C (44.78%), H (3.98%)

6.2.8 Ru4I'

The procedure was the same used to obtain **Ru1I** but starting from **Ru5Cl'** (240 mg, 0.42 mmol) and keeping the reaction 11 days at reflux. Yield: 116 mg (37%).

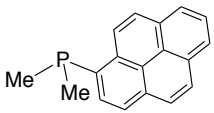


Brown solid. **IR**: 3065, 3035, 1935, 1733, 1288, 1270, 913, 849. **^{31}P{^{1}H} NMR**: δ –5.2 (s). **^{1}H NMR**: δ 9.31 (d, *J* = 9.6, 1H), 8.51-8.10 (m, 8H), 6.25 (s, br, 2H), 5.70 (t, *J* = 5.6, 1H), 4.91 (s, br, 2H), 3.90 (s, 3H), 2.49 (d, *J* = 9.6, 6H). **^{13}C{^{1}H} NMR**: δ 165.2 (CO), 130.5-123.9 (C, CH, Ar), 93.0 (CH), 53.0 (CH_3), 20.4 (CH_3). **HRMS** (ESI): *m/z* calc. for $C_{26}H_{23}IO_2PRu$ $[M - I]^+$ 626.9518; found 626.9518. **EA**: calc. for $C_{26}H_{23}I_2O_2PRu$ C (41.45%), H (3.08%); found C (41.25%), H (3.32%).

6.3. PREPARATION OF PHOSPHINES

6.3.1. L4

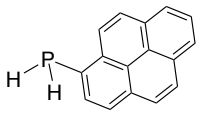
MeMgCl (3.3 mL, 3 M in THF, 10 mmol) was added to a solution of **L0** (1.5 g, 5 mmol) in THF (50 mL) previously cooled to –78 ºC, stirred for 3 h and the mixture was allowed to warm up to room temperature. At this point, the reaction was quenched with MeOH (1 mL) and the solution of the phosphine was ready to be used.



Orange solution. **^{31}P{^{1}H} NMR**: δ –59.7 (inset).

6.3.2. L5

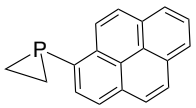
To a suspension of $LiAlH_4$ (382 mg, 10.1 mmol) in THF (40 mL) cooled at –78 ºC, **L0** (1.5 g, 5 mmol) dissolved in THF (30 mL) was added dropwise during 2 h and the mixture was allowed to reach room temperature overnight. To the brown suspension a thoroughly degassed aqueous solution of NH_4Cl was carefully added and the THF was eliminated under vacuum. Always under N_2, the mixture was extracted with dichloromethane, the organic phase dried with Na_2SO_4, decanted and the solvent removed under reduced pressure to give a yellow product. Yield 888 mg (76%).



Yellow solid. **$^{31}P\{^1H\}$ NMR**: δ –129.7 (s). **^{31}P NMR**: δ –129.7 (tdt, *J* = 204.3, *J* = 7.3, *J* = 1.1). **^1H NMR**: δ 8.41 (dd, *J* = 9.2, *J* = 2.0, 1H), 8.23-7.99 (m, 8H), 4.45 (d, *J* = 204, 2H). **$^{13}C\{^1H\}$ NMR**: δ 133.7-122.6 (C, CH, Ar).

6.3.3. L6

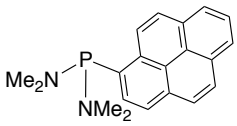
MeLi (2.6 mL, 1.6 M in diethyl ether, 4.18 mmol) was added to a suspension of **L5** (445 mg, 1.9 mmol) in THF (10 mL) precooled at –78 ºC and the purple solution was stirred for 30 min. 1,2-Dichloroethane (0.18 mL, 2.28 mmol) was added and the mixture was allowed to reach room temperature overnight. The reaction was quenched with MeOH (1 mL) and the THF was eliminated under vacuum. Always under N_2, the mixture was extracted with dichloromethane, the organic phase dried with Na_2SO_4, decanted and the solvent removed under reduced pressure to give a yellow product. Yield 452 mg (91%).



Yellow solid. **$^{31}P\{^1H\}$ NMR** (C_6D_6): δ –235.8 (s). **^1H NMR** (C_6D_6): δ 9.00 (dd, *J* = 9.2, *J* = 2.8 1H), 7.91-7.68 (m, 8H), 1.29-1.25 (m, 2H), 1.16-1.08 (m, 2H). **$^{13}C\{^1H\}$ NMR** (C_6D_6): δ 136.8-124.7 (C, CH, Ar), 10.8 (d, *J* = 40.8, $2CH_2$).

6.3.4. L7

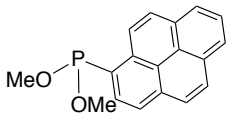
NEt_3 (2.0 mL, 14 mmol) and $HNMe_2$ (2.6 mL, 5.2 mmol) were subsequently added to a suspension of **L0** (758 mg, 2.5 mmol) in THF (30 mL) and the solution was stirred overnight. The crude product was filtered and the solvent removed under reduced pressure to give a yellow product. Yield 755 mg (94%).



Yellow solid. **$^{31}P\{^1H\}$ NMR**: δ +100.9 (s). **^1H NMR**: δ 8.57 (d, *J* = 9.2, 1H), 8.21-7.98 (m, 8H), 2.86 (d, *J* = 8.8, 12H). **$^{13}C\{^1H\}$ NMR**: δ 134.8-124.3 (C, CH, Ar), 41.6 (d, *J* = 16.3, $4CH_3$).

6.3.5. L8

NEt_3 (2.0 mL, 14 mmol) and MeOH (0.25 mL, 5.5 mmol) were subsequently added to a solution of **L0** (758 mg, 2.5 mmol) in dichloromethane (20 mL) and the solution was stirred for 2 h. The suspension was filtered and the filtrate was concentrated to dryness under reduced pressure to give a yellow product. Yield 582 mg (79%).



Yellow solid. **$^{31}P\{^1H\}$ NMR**: δ +159.7 (s). **^1H NMR**: δ 8.68 (dd, *J* = 9.2, *J* = 3.6, 1H), 8.29 (dd, *J* = 7.6, *J* = 3.2, 1H), 8.07-7.84 (m, 7H), 3.52 (d, *J* = 10.8, 6H). **$^{13}C\{^1H\}$ NMR**: δ 133.0-123.7 (C, CH, Ar), 53.5 (d, *J* = 9.8, $2CH_3$).

7. CONCLUSIONS

- The iodinated ruthenium complexes (**Ru1**-**Ru4**) were successfully obtained from the analogous chloro complexes by substitution with sodium iodide.
- The reaction rate strongly depends on the starting complex structure. Those containing the *p*-cymene group react faster than those with the methyl benzoate. Regarding the phosphine, unhindered ancillary ligands give slower reactions. Unfortunately, long reaction times produce low yields due to the decomposition of the complexes.
- In ^{1}H NMR of some complexes, extra peaks were observed, which may belong to the presence of different rotamers.
- The preliminary cytotoxicity studies of **Ru1I** against several cell lines show that this complex is more active than **Ru1Cl**.
- From the described precursor **L0**, new 1-pyrenylphospine ligands (**L4**-**L8**) were obtained following literature methods for similar substrates.

8. REFERENCES AND NOTES

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9. ACRONYMS

EA: Elemental Analysis

HRMS: High Resolution Mass Spectroscopy

HSQC: Heteronuclear Single Quantum Coherence spectroscopy

IC_{50}: Half Maximal Inhibitory Concentration

IR: Infrared spectroscopy

NMR: Nuclear Magnetic Resonance

THF: Tetrahydrofuran

XRD: X-Ray Diffraction